REMARKS

Claims 1-21 are pending in the instant application. Claims 1-9 and 19-21 have been rejected. Claims 10-18 have been objected to. Claims 1-6 have been amended. Support for these amendments can be found in the specification on page 19, lines 17-20. New Claims 22-31 have been added. There is no new subject matter being added, and support for these claims can be found throughout the specification. Upon entry of this amendment, Claims 1-31 will be pending.

Rejection of Claims 1-9 under 35 USC §103(a)

The Examiner has rejected Claims 1-9 under 35 USC §103(a) as being unpatentable over Conn et al US 4,704,472 taken with Pietruszkiewicz et al US 4,835,313. Specifically, the Examiner states that:

> Conn et al US '472 teach fluorenone derivatives of the type recited in the claims. For example, where applicants' formula in claim 1, X=O, R6 = RO, R3 = chloro and R10= C3 alkyl. See column 1 line 35+ and claim 1. Patentees differ from in that they do not recite all possible combinations falling within the scope of the recited claims. However, Pietruszkiewicz et al US '313 teach that the other analogous compounds would have been obvious to one of ordinary skill in the art due to the close structural relationship between the compounds. This is particularly true in light of the similar utilities between the references, which would give one a reason to modify Conn et al US '472. It is further noted that the claimed compounds would have been obvious notwithstanding any intended use.

Applicants respectfully traverse the Examiner's rejection.

The present invention claims novel tetrahydrofluorenone derivatives that have use as estrogen receptor modulators. The compounds of the present invention exhibit estrogenic effects through a mechanism that includes binding to the estrogen receptors. This binding is affected by the particular substitution patterns on the tetrahydrofluorenone ring.

The Conn and Pietruszkiewicz patents teach fluorenone derivatives that have use as neuroprotective drugs. The compounds in these patents reduce brain edema via an anion transport inhibition mechanism. These compounds are able to regulate the chloride channels in astrocyte cells because of their specific substitution patterns.

The pharmaceutical sciences are highly unpredictable, and it is difficult to predict the level of activity a compound will have in a particular assay merely by looking at it. After reviewing the Conn and Pietruszkiewicz patents, one would note that substitution patterns at the 4 and 7 positions appear to affect the activity of the compounds in the brain edema assay. Thus, one skilled in the art would expect that these compounds might have utility for the treatment of brain edema. When compared with the compounds disclosed in the Conn and Pietruszkiewicz patents, the compounds of the present invention have different substitution patterns at the 4 and 7 positions of the tetrahydrofluorenone ring. After reading the Conn and Pietruszkiewicz patents, one skilled in the art would not be motivated to make the compounds of the present invention for the treatment of *any disorder*, including the treatment of brain edema or estrogen modulation.

Furthermore, one of ordinary skill in the art would not expect the compounds described in the Conn and Pietruszkiewicz patents to be effective for any other indication than the treatment of brain edema or for anion transport regulation in astrocyte cells. The Conn and Pietruszkiewicz patents do not teach the use of fluorenone derivatives for the treatment of estrogen related disorders, and as such one would not be motivated to use the compounds disclosed in the Conn and Pietruszkiewicz patents for estrogen receptor modulation. Accordingly, because the Conn and Pietruszkiewicz patents do not teach estrogen receptor modulating compounds, one of ordinary skill in the art would not look to these teachings for direction on how to make compounds that can be used as estrogen receptor modulators.

Thus, it cannot be said that the estrogen receptor modulating compounds of the present invention could be obvious after reading the Conn and Pietruszkiewicz patents because the fluorenones in the cited references contain very different substitution at the 4 and 7 position, and the cited references do not teach estrogen receptor modulating compounds. Therefore, Applicants

respectfully request the rejection of claims 1-9 under 35 USC §103(a) be withdrawn.

Rejection of Claims 19-21 under 35 USC §112, first paragraph

The Examiner has rejected the specification under 35 USC §112, first paragraph, as not giving any guidance as to the full range of conditions which could be treated or prevented using the instant claimed process. Specifically, the Examiner stated that:

> In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 25 U.S.C. §112, first paragraph, have been described. They are: 1. nature of the invention, 2. the state of the prior art, 3. the predictability or lack thereof in the art, 4. the amount of direction or guidance present, 5. The presence or absence of working examples, 6. the breadth of the claims, 7. the quantity of experimentation needed, and 8. the level of skill in the art.
>
> In the instant case, Applicants are claiming a method of preventing hot flashes, anxiety or depression. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles established that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant specification does not give any guidance as to how the instant claimed process effects the full range modalities and mechanisms necessary to completely prevent the conditions claimed i.e. more then one thing causes, for example, depression. In order to practice the claimed invention, one skilled in the art would have to speculate which conditions could be prevented using the claimed compounds found in the instant claims. The number of possible conditions embraced by the claims would impose undue experimentation on the skilled art worker. Therefore the broad terminology treatment or

prevention is not enabled because the metes and bounds of conditions that could be treated or prevented cannot be ascertained.

Applicants respectfully traverse the Examiner's rejection.

Applicants claim methods of treatment or prevention of hot flashes, depression and anxiety. Since the compounds of the present invention act as estrogen receptor modulators, one skilled in the art would understand that these conditions are treated via a mechanism that includes estrogen receptor modulation. Applicants are not required to submit a detailed description of the modalities and mechanisms involved in hot flashes, anxiety or depression.

Applicants also traverse the Examiner's assertion that "the broad terminology treatment or prevention is not enabled because the metes and bounds of conditions ...cannot be ascertained." In Claim 19, Applicants claim the treatment or prevention of hot flashes. One skilled in the art would understand the meaning of "treatment or prevention of hot flashes" and discern the metes and bounds of the statement. In Claim 20, Applicants claim the treatment or prevention of anxiety. One skilled in the art would understand the meaning of "treatment or prevention of anxiety" and discern the metes and bounds of the statement. In Claim 21, Applicants claim the treatment or prevention of depression. One skilled in the art would understand the meaning of "treatment or prevention of depression" and discern the metes and bounds of the statement.

Furthermore, there are many assays known to those skilled in the art which would enable one to use the invention without undue experimentation. For example, one skilled in the art could use a rat forced-swim assay to screen for compounds useful in the treatment of depression or a resident intruder assay to screen for compounds useful in the treatment of anxiety.

Accordingly, Applicants respectfully request that the rejection of Claims 19-21 under 35 USC §112, first paragraph be withdrawn.

<u>Rejection of Claims 19-21 under 35 USC §112, first paragraph</u>

The Examiner has rejected Claims 19-21 under 35 USC §112, first paragraph, on the grounds of insufficient disclosure of utility. The Examiner states that "the terminology 'treating or preventing hot flashes, anxiety or

depression' not believable in view of the contemporary knowledge of the art for the reasons set forth in the next above paragraph."

Applicants respectfully traverse this rejection. The Examiner bears the initial burden of challenging Applicants' asserted utility, see MPEP §2164.08. The Examiner has not provided any evidence to disprove Applicants' assertion that the compounds and compositions of the present invention are estrogen receptor modulators and have therapeutic utility as treatment for hot flashes, depression and anxiety. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 19-21 under 35 USC §112, first paragraph.

Rejection of Claims 1-21 under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-21 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that:

> The specification does not give any guidance as to how each of the derivatives were prepared. In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 25 U.S.C. §112, first paragraph, have been described. They are: 1. nature of the invention, 2. the state of the prior art, 3. the predictability or lack thereof in the art, 4. the amount of direction or guidance present, 5. The presence or absence of working examples, 6. the breadth of the claims, 7. the quantity of experimentation needed, and 8. the level of skill in the art.
>
> In the instant case, Applicants are claiming derivatives. Applicants have not disclosed any working examples which would demonstrate, or guide, one skilled in the art as to how these derivatives were prepared or obtained, the process of making these derivatives or how they were obtained is not readily apparent from the specification.

> The specification must teach how to make the invention. In re Gardner, 166 U.S.P.Q. 138 (1970). In order to practice the claimed invention, one skilled in the art would have to speculate how the derivatives were obtained or prepared. Therefore, the instant invention is not enabled.
>
> ...
>
> The exemplification of two heteroaryl groups, namely thiophenyl and furanyl, is no way supportive of the vast number of known heterocyclic groups encompassed by the claims as presently recited. For example, the disclosed heteroaryl examples would not suggest how to make or use derivatives containing quinoline, benzopyrimidine, morpholine, oxathiazines and other heteroaryl groups.

Applicants respectfully traverse this rejection. Applicants assert that the specification does enable the claims and provides ample guidance as to how substituted derivatives are prepared.

In order to make a rejection based upon lack of enablement, *the Examiner has the initial burden* to establish a reasonable basis to question the enablement provided for the claimed invention (MPEP §2164.04). "A specification disclosure which contains a teaching...must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first parpagraph, *unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support*" (MPEP 2164.04, emphasis added). The Examiner has still not met the initial burden of establishing a reasonable basis to question the enablement provided in the specification.

The Examiner states that "Applicants have not disclosed any working examples, which would demonstrate or guide one skilled in the art as to how these derivatives were prepared or obtained, the process of making these derivatives or how they were obtained is not readily apparent from the specification." Applicants disagree with the Examiner's allegation. As long as the specification discloses at least one method for making or using the invention that bears a reasonable correlation to the scope of the claims, the enablement requirement is

satisfied, see MPEP § 2164.01(b). Applicants have provided much more than one method for making or using the invention; Applicants have provided eight generic schemes that can be used for guidance in making the compounds of the present invention and have included thirty-five working examples, complete with reaction conditions and characterization data for the title compounds and intermediates. In addition, Applicants have provided characterization data for over 100 compounds. These examples clearly demonstrate to one skilled in the art as to how various "derivatives" were prepared or obtained and the process for making these derivatives. Even though the nature of the invention is in the chemical arts and there is limited predictability in the field, "the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required" (MPEP § 2164.03, emphasis added). One skilled in the art, after reading the disclosure in the present application, would be able to make and use the compounds and compositions encompassed by the claims.

Applicants maintain that the Examiner has not made a prima facie case of nonenablement, and in light of the arguments presented, it is not reasonable to conclude that Applicant has not enabled the claims. Accordingly, Applicants respectfully request the rejection of claims 1-21 under 35 USC §112, first paragraph, be withdrawn. Applicants maintain that the application is in condition for allowance and passage to issue is earnestly requested.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

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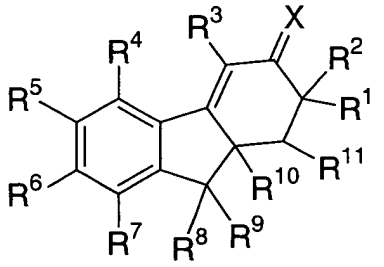
VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice amended) A compound of the formula:



wherein X is selected from the group consisting of: O, N-OR^a, N-NR^{a}R^b and C_{1-6} alkylidene, wherein said alkylidene group is unsubstituted or substituted with a group selected from hydroxy, amino, O(C_{1-4}alkyl), NH(C_{1-4}alkyl), or N(C_{1-4}alkyl)$_2$;

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein said alkyl, alkenyl and alkynyl groups are either unsubstituted or substituted with a group selected from OR^c, SR^c, NR^{b}R^c ,C(=O)R^c, C(=O)CH_2OH, or phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, O(C_{1-4}alkyl), NH_2, NH(C_{1-4}alkyl), NH(C_{1-4}alkyl)$_2$, halo, CN, NO_2, CO_2H, CO_2(C_{1-4}alkyl), C(O)H, and C(O)(C_{1-4}alkyl);

R^2 is selected from the group consisting of hydrogen, hydroxy, iodo, O(C=O)R^c, C(=O)R^c, CO_2R^c, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein said alkyl, alkenyl and alkynyl groups are either unsubstituted or substituted with a group selected from OR^c, SR^c, NR^{b}R^c ,C(=O)R^c, C(=O)CH_2OH, or phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, O(C_{1-4}alkyl), NH_2, NH(C_{1-4}alkyl), NH(C_{1-4}alkyl)$_2$, halo, CN, NO_2, CO_2H, CO_2(C_{1-4}alkyl), C(O)H, and C(O)(C_{1-4}alkyl);

or R^1 and R^2, when taken together with the carbon atom to which they are attached, form a carbonyl group;
or R^1 and R^2, when taken together, form a C_{1-6} alkylidene group, wherein said alkylidene group is either unsubstituted or substituted with a group selected from the group consisting of hydroxy, $O(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of $C_{1-4}alkyl$, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;

R^3 is selected from the group consisting of fluoro, chloro, bromo, iodo, cyano, NR^aR^c, OR^a, $C(=O)R^a$, CO_2R^c, $CONR^aR^c$, SR^a, $S(=O)R^a$, SO_2R^a, $C_{1-10}alkyl$, $C_{2-10}alkenyl$, $C_{2-10}alkynyl$, $C_{3-7}cycloalkyl$, 4-7 membered heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl groups are either unsubstituted or independently substituted with 1, 2 or 3 groups selected from fluoro, chloro, bromo, iodo, cyano, OR^a, NR^aR^c, $O(C=O)R^a$, $O(C=O)NR^aR^c$, $NR^a(C=O)R^c$, $NR^a(C=O)OR^c$, $C(=O)R^a$, CO_2R^a, $CONR^aR^c$, $CSNR^aR^c$, SR^a, $S(O)R^a$, SO_2R^a, $SO_2NR^aR^c$, YR^d, and ZYR^d;

R^4 is selected from the group consisting of hydrogen and fluoro;

R^5 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, methyl, amino, OR^b, OR^a, $O(C=O)R^c$, $O(C=O)OR^c$, and $NH(C=O)R^c$;

R^6 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, methyl, OR^b, OR^a, $O(C=O)R^c$, and $O(C=O)OR^c$;

R^7 is selected from the group consisting of hydrogen, OR^b, NR^bR^c, fluoro, chloro, bromo, iodo, cyano, nitro, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, CF_3, and CHF_2;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$,
or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a 3-5 membered cycloalkyl ring,

or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a carbonyl group;

R^{10} is selected from the group consisting of hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups can be optionally substituted with a group selected from chloro, bromo, iodo, OR^b, SR^b, $C(=O)R^b$, or 1-5 fluoro,

or R^{10} and R^1, when taken together with the three intervening carbon atoms to which they are attached, form a 5-6 membered cycloalkyl or cycloalkenyl ring which can be optionally substituted with 1 or 2 groups selected from oxo, hydroxy, or C_{1-6}alkyl;

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^a is selected from the group consisting of hydrogen, C_{1-10}alkyl, and phenyl, wherein said alkyl group can be optionally substituted with a group selected from hydroxy, amino, $O(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, phenyl, or 1-5 fluoro, and

wherein said phenyl groups can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;

R^b is selected from the group consisting of hydrogen, C_{1-10}alkyl, benzyl and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;

R^c is selected from the group consisting of hydrogen, C_{1-10}alkyl and phenyl, wherein said phenyl group can either be unsubstituted or substituted with 1-3 substituents independently selected from the group consisting of C_{1-4}alkyl, OH, $O(C_{1-4}alkyl)$, NH_2, $NH(C_{1-4}alkyl)$,

$NH(C_{1-4}alkyl)_2$, halo, CN, NO_2, CO_2H, $CO_2(C_{1-4}alkyl)$, C(O)H, and $C(O)(C_{1-4}alkyl)$;
or R^a and R^c, whether or not on the same atom, can be taken together with any attached and intervening atoms to form a 4-7 membered ring;

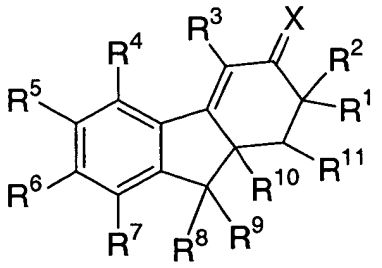
R^d is selected from the group consisting of NR^bR^c, OR^a, CO_2R^a, $O(C=O)R^a$, CN, $NR^c(C=O)R^b$, $CONR^aR^c$, $SO_2NR^aR^c$, and a 4-7 membered N-heterocycloalkyl ring that can be optionally interrupted by O, S, NR^c, or C=O;

Y is selected from the group consisting of CR^bR^c, C_{2-6} alkylene and C_{2-6} alkenylene, wherein said alkylene and alkenylene linkers can be optionally interrupted by O, S, or NR^c;

Z is selected from the group consisting of O, S, NR^c, C=O, O(C=O), (C=O)O, $NR^c(C=O)$ or $(C=O)NR^c$;

~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.

2. (Twice Amended) A compound of the formula:



wherein X is selected from the group consisting of O and $N\text{-}OR^a$;

R^1 is selected from the group consisting of hydrogen and C_{1-6}alkyl, wherein said alkyl group is either unsubstituted or substituted with a group selected from OR^c or $C(=O)R^c$;

R^2 is selected from the group consisting of hydrogen, hydroxy, iodo, and C_{1-6}alkyl, wherein said alkyl group is either unsubstituted or substituted with a group selected from OR^c or $C(=O)R^c$;

R^3 is selected from the group consisting of chloro, bromo, iodo, cyano, C_{1-10}alkyl, C_{2-10}alkenyl, aryl and heteroaryl, wherein said alkyl, alkenyl, aryl and heteroaryl groups are either unsubstituted or

independently substituted with 1, 2 or 3 groups selected from fluoro, chloro, bromo, iodo, cyano, OR^a, NR^aR^c, $C(=O)R^a$, CO_2R^c, $NR^aC(=O)R^c$, $CONR^aR^c$, $CSNR^aR^c$, SR^a, YR^d, and ZYR^d;

R^4 is selected from the group consisting of hydrogen and fluoro;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, fluoro, $O(C=O)R^c$ and OR^a;

R^7 is selected from the group consisting of hydrogen, NR^bR^c, chloro, bromo, nitro and C_{1-6}alkyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen and C_{1-6}alkyl;
or R^8 and R^9, when taken together with the carbon atom to which they are attached, form a carbonyl group;

R^{10} is selected from the group consisting of hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-6}cycloalkyl and cycloalkylalkyl, wherein said alkyl, alkenyl, cycloalkyl and cycloalkylalkyl groups can be optionally substituted with a group selected from OR^b, SR^b, $C(=O)R^b$, or 1-5 fluoro;
or R^{10} and R^1, when taken together with the three intervening carbon atoms to which they are attached, form a 5-6 membered cycloalkyl ring which can be optionally substituted with C_{1-6}alkyl;

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^a is selected from the group consisting of hydrogen, C_{1-10}alkyl, and phenyl, wherein said alkyl group can be optionally substituted with a group selected from hydroxy, amino, $O(C_{1-4}alkyl)$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, phenyl, or 1-5 fluoro;

R^b is selected from the group consisting of hydrogen, C_{1-10}alkyl, benzyl and phenyl;

R^c is selected from the group consisting of hydrogen and C_{1-10}alkyl and phenyl;
or R^a and R^c, whether or not on the same atom, can be taken together with any attached and intervening atoms to form a 4-7 membered ring;

R^d is selected from the group consisting of NR^bR^c, OR^a, CO_2R^a, $O(C=O)R^a$, CN, $NR^c(C=O)R^b$, $CONR^aR^c$, $SO_2NR^aR^c$, and a 4-7 membered N-heterocycloalkyl ring that can be optionally interrupted by O, S, NR^c, or C=O;

Y is selected from the group consisting of CR^bR^c, C_{2-6} alkylene and C_{2-6} alkenylene, wherein said alkylene and alkenylene linkers can be optionally interrupted by O, S, or NR^c;

Z is selected from the group consisting of O, S, NR^c, C=O, O(C=O), (C=O)O, NR^c(C=O) or (C=O)NR^c;

~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.

3. (Amended) ~~A~~ The compound according to Claim 2, wherein X is selected from the group consisting of O, N-OH and N-OCH_3, ~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.

4. (Amended) ~~A~~ The compound according to Claim 3, wherein R^6 is selected from the group consisting of OR^a and O(C=O)R^c ~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.

5. (Amended) ~~A~~ The compound according to Claim 4, wherein R^3 is selected from the group consisting of hydrogen, chloro, bromo, iodo, cyano, C_{1-10}alkyl, aryl and heteroaryl, wherein said alkyl, aryl and heteroaryl groups are either unsubstituted or independently substituted with 1, 2 or 3 groups selected from fluoro, chloro, bromo, cyano, NR^aR^c, C(=O)R^a, CO_2R^c, $CONR^aR^c$, SR^a, YR^d, and ZYR^d , ~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.

6. (Amended) ~~A~~ The compound according to Claim 1 selected from the group consisting of:

4-bromo-7-hydroxy-9a-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(3*E*)-9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one oxime;

9a-[(1*E*)-1-butenyl]-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-9a-butyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-9a-butyl-3-methylene-2,3,9,9a-tetrahydro-1*H*-fluoren-7-ol;

9a-butyl-4-cyano-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-benzyl-9a-butyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a butyl-7-hydroxy-4-(2-thienyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-ene;

9a-butyl-7-hydroxy-4-{4-[2-(1-piperidinyl)ethoxy]phenyl}-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-7-hydroxy-4-(4-hydroxyphenyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*E*)-3-[4-(9a-butyl-7-hydroxy-3-oxo-2,3,9,9a-tetrahydro-1*H*-fluoren-4-yl)phenyl]-2-propenoic acid;

9a-butyl-7-hydroxy-8-methyl-1,2,9,9a-3*H*-tetrahydro-fluoren-3-one;

4-bromo-9a-butyl-7-hydroxy-8-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a butyl-4,8-dimethyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-9a-butyl-2,4-dimethyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*RS*)-9a-butyl-2,4-dimethyl-7-hydroxy-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-2,2,4-trimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*RS*)-9a-butyl-7-hydroxy-2-iodo-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*RS*)-9a-butyl-2,7-dihydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*RS*,9a*SR*)-9a-butyl-7-hydroxy-2-(2-hydroxyethyl)-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-2-allyl-9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*RS*,9a*SR*)-9a-butyl-7-hydroxy-2-(3-hydroxy-2-oxopropyl)-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(9*SR*,9a*SR*)-7-hydroxy-4-methyl-9-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-7-hydroxy-4-(trifluoromethyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-acetyl-9a-butyl-8-chloro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-4-cyano-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-ethyl-6-fluoro-7-hydroxy-8-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-6-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-4-ethyl-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-9a-butyl-8-chloro-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-6-fluoro-7-hydroxy-4-(trifluoromethyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

2-hydroxy-5-methylgibba-1(10a),2,4,4b-tetraen-6-one;

4-bromo-9a-butyl-3-oxo-2,3,9,9a-1*H*-fluoren-7-yl pivalate;

7-hydroxy-4,9a-dimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-hydroxy-4-methyl-9a-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-hydroxy-9a-isobutyl-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-ethyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4,9a-dibutyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-chloro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-iodo-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-trifluoromethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-phenyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-(2-furyl)-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-hydroxy-9a-(3-iodopropyl)-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-hydroxy-4-methyl-9a-(2-methyl-1-propenyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-{4-[2-(dimethylamino)ethoxy]phenyl}-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-4-{4-[2-(diethylamino)ethoxy]-phenyl}-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-7-hydroxy-4-{4-[2-(1-pyrrolidinyl)ethoxy]phenyl}-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-7-hydroxy-4-{4-[2-(4-morpholinyl)ethoxy]phenyl}-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-4-{4-[3-(dimethylamino)propoxy]-phenyl}-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

9a-butyl-7-hydroxy-4-{4-[3-(1-piperidinyl)propoxy]phenyl}-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one hydrochloride;

(3*E*)-9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one *O*-methyloxime;

(2*SR*,9a*SR*)-9a-butyl-2-ethyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-9a-butyl-7-hydroxy-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-9a-butyl-7-hydroxy-4-methyl-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-4,9a-dibutyl-7-hydroxy-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-4-bromo-9a-butyl-7-hydroxy-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*RS*,9a*SR*)-9a-butyl-7-hydroxy-2-(2-oxoethyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-2,9a-dibutyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*RS*,9a*RS*)-9a-butyl-7-hydroxy-2,4-dimethyl-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-2,2-dipropyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-methyl-2,2-dipropyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*RS*)-9a-butyl-2,7-dihydroxy-4-methyl-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-9a-butyl-2,2-diethyl-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-7-hydroxy-2,4,9a-trimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-7-hydroxy-4,9a-dimethyl-2-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

(2*SR*,9a*SR*)-9a-butyl-8-chloro-2-ethyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-chloro-9a-ethyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-ethyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-7-hydroxy-4,8-dimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-chloro-7-hydroxy-4-methyl-9a-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-7-hydroxy-4-methyl-9a-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-hydroxy-4,8-dimethyl-9a-propyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-chloro-7-hydroxy-4-methyl-9a-[(1*E*)-1-propenyl]-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4,8-dimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-4-methyl-8-nitro-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-amino-9a-butyl-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;
9a-butyl-7-hydroxy-4-(4-hydroxyphenyl)-8-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-7-hydroxy-8-methyl-4-{4-[2-piperidinyl)-ethoxy]phenyl}-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-7-hydroxy-9a-propyl-1*H*-fluorene-3,9(2*H*,9a*H*)-dione;

4,8-dibromo-7-hydroxy-9a-propyl-1*H*-fluorene-3,9(2*H*,9a*H*)-dione;

4-bromo-9a-butyl-7-hydroxy-6-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-8-chloro-4-methyl-3-oxo-2,3,9,9a-tetrahydro-1*H*-fluoren-7-yl pivalate;

9a-butyl-6,8-difluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4-ethyl-6,8-difluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-9a-butyl-6,8-difluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-butyl-4-chloro-8-difluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-butyl-4,8-dibromo-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6,8-difluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-chloro-9a-ethyl-6-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-ethyl-6-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6-fluoro-7-hydroxy-4,8-dimethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4,9a-diethyl-6,8-difluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-8-chloro-9a-ethyl-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-bromo-8-chloro-9a-(cyclopentylmethyl)-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-5-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-ethyl-5-fluoro-7-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6,7-dihydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

8-bromo-9a-ethyl-6,7-dihydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6-hydroxy-4-methyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

9a-ethyl-6-hydroxy-4-vinyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

4-allyl-9a-ethyl-6-hydroxy-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

2-hydroxy-5-methyl-7,8,9,10-tetrahydro-7,10a-methanocycloocta[*a*]inden-6(11*H*)-one;

7-amino-4-bromo-9a-butyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

7-amino-4,8-dibromo-9a-ethyl-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one;

~~and the~~ or a pharmaceutically acceptable salts or stereoisomer thereof.